Status Update of Systematic Review Approaches for Human Health Information

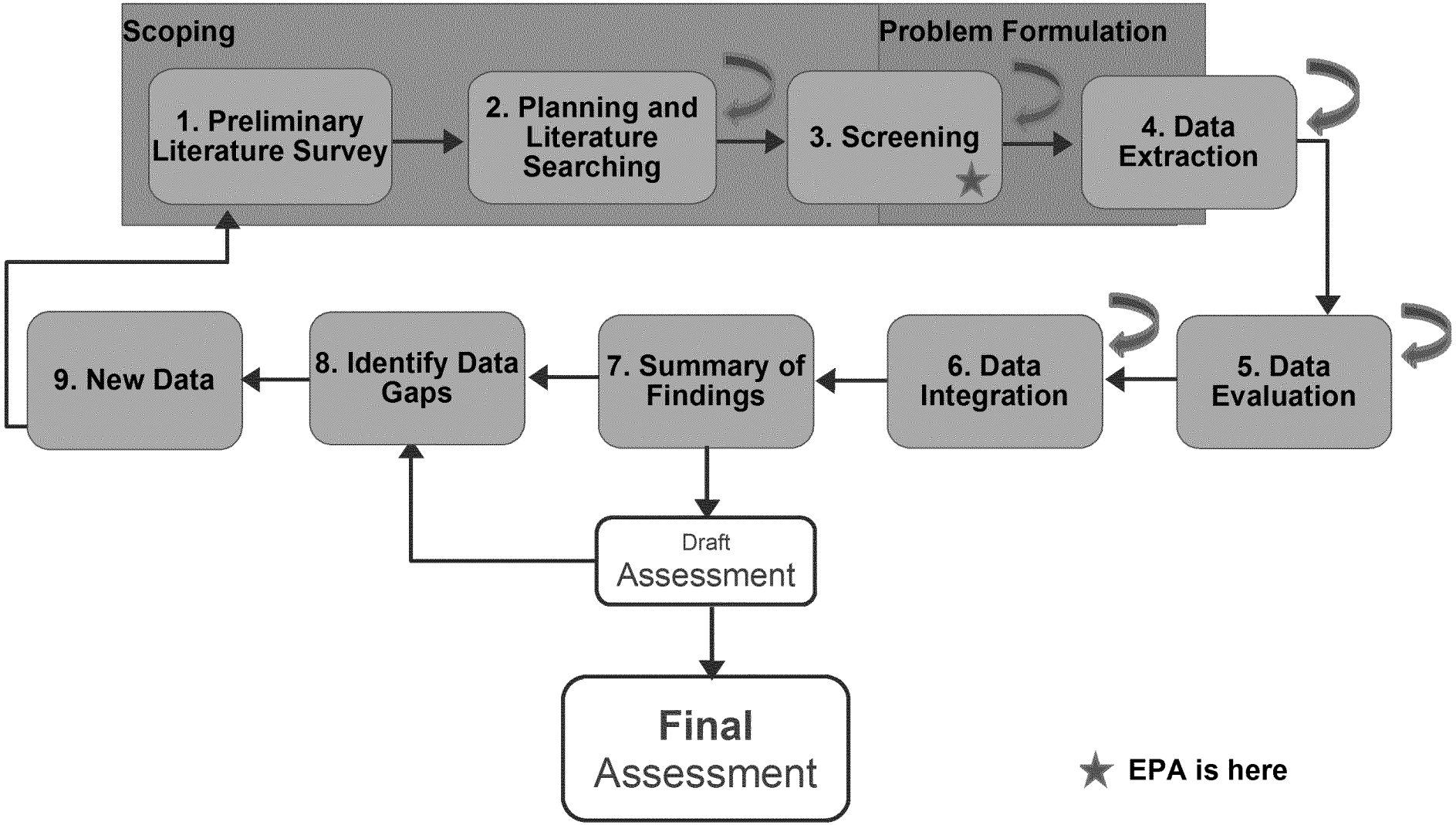
August 30, 2017

Risk Assessment Division

Outline

- Full-Text Screening
  - Pilot
  - Scale Up
- Targeted Data Searches/Additional Screening
- Data Extraction
- Data Quality Review
- Timeline

Overview OPPT's Systematic Review Process for First Ten Existing Chemicals Evaluations



References to be Reviewed

Chemical	All Peer-Reviewed		Post-IRIS/ROC Peer-Reviewed[1]		Gray Literature	
	Off Topic	On Topic	Off Topic	On Topic	Off Topic	On Topic
1,4 Dioxane	1,481	140	1,374	24	999	59
1-Bromopropane	397	123	321	43	263	30
Asbestos [2]	9,256	10,938	N/A	N/A	2,855	70
Carbon Tet [3]	3,155	2,751	2,901	2,374	1,238	36
HBCD	863	311	32	14	676	40
Methylene Chloride	5,237	372	5,098	130	1,722	36
NMP	651	121	N/A	N/A	598	27
Perchloroethylene	2,095	732	689	85	2,078	34
Pigment Violet 29	219	-	N/A	N/A	233	2
Trichloroethylene	3,781	1,347	2,867	374	2,251	58
Total	27,135	16,835	13,282	3,044	12,913	392

1 Asbestos, NMP, and PV29 do not have IRIS or RoC assessments

2 RAD proposes to review a subset of asbestos articles (i.e., will exclude any studies that did not evaluate cancer in humans exposed via inhalation).

3 RAD proposes to review a subset of carbon tet articles (e.g., will *exclude* articles where carbon tet is used as a control for studies evaluating therapeutic agents).

Full-Text Screening: Pilot

- Drafted inclusion/exclusion criteria for the first 10 chemicals to guide screening
- Developing Distiller forms and guidance for screeners
- Will review a subset of articles to determine need to refine screening criteria
- Will provide a solid foundation for scaling up

Full-Text Screening: Scale Up

- Literature with pdfs available - Use HERO link in Distiller
- Literature with no pdfs available - may use two tiered process:
  - First review title and abstract with pre-defined criteria to determine whether we want the pdf
  - Then screen once pdfs becomes available
- EPA will screen ~ 10% and contractor will screen ~90% of the articles
- EPA will need to manage Distiller licenses and assign articles on a rotating basis
- EPA will resolve conflicts and update the screening guidance document

Targeted On-Topic Data Searches/Screening

- After categorizing current on-topic studies, RAD will/may do additional targeted searching/screening:
  - Searching off-topic references using additional keywords, machine learning and secondary sources to identify articles that could be on-topic
  - Updating the search using a similar approach as original search
  - Searching for data not necessarily specific to the chemical, such as:
    - Prevalence in humans of the health outcome(s) evaluated
    - General data on mechanisms (e.g., the newest PPAR-alpha research) to understand relevance to humans.
- Any new search strategies will be developed, reviewed and documented by the team prior to initiation.
- Some searches/screening will be done during the analysis phase.

Data Extraction

- Three main questions:
  - What data elements to extract?
  - Where to extract them?
  - When to extract?
- What data elements to extract?
  - Crosswalk with OECD Harmonized Templates (OHTs 58-83 and 86)

    http://www.oecd.org/ehs/templates/harmonised-templates-health-effects.htm
  - Determine what will/will not be needed for risk evaluation

Data Extraction

- Where to extract them?
  - Possibly into one of the following programs:
    - Distiller (can track work flow)
    - HAWC (can provide study quality evaluation and visualization of data for human health, and possibly other endpoints (future))
  - Need appropriate tables etc. for risk evaluation document
  - Export into IUCLID (international database)
- When to extract?
  - Before or after data quality review
  - Efficiencies if done beforehand but may be resource intensive for chemicals with a lot of data

Data Quality Review

- Internal validity or risk of bias
  - Assess credibility of results based on design/conduct of study
  - Consider individual types of bias (selection, reporting, etc.)
- External validity or directness and applicability
  - Assess how well study addresses topic under review
  - Was study design able to assess endpoints of concern for relevant chemical class?
- Reporting quality - assess completeness of reported study details
- Different criteria depending on type of data
  - Epidemiological studies, biomonitoring data
  - Animal toxicity studies
  - *In vitro* studies, high throughput data
- Consider options for chemicals with only limited data that may be of lower quality

Refs consulted: Rooney et al. 2014; Hoffman et al. 2017

Data Quality Review Criteria: Example Sources

- Application of Systematic Review Methods…Endocrine Active Chemicals (NRC 2017)
- Review of EPA's Integrated Risk Information System (IRIS) Process (NRC 2014)
- OPP's Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides (EPA 2016)
- Handbook for Developing IRIS Assessments (in development)
- Guidelines for Carcinogen Risk Assessment (EPA 2005) and other Risk Assessment Forum guidance documents
- Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994)
- Handbook for conducting a Literature-based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (NTP 2015)
- Published articles on systematic review; other NRC reports

Full Screening SysRev Timeline

- Pilot:
  - Targeted for completion in September
- Full-text screen of post-IRIS/RoC references:
  - Seven of the 10 chemicals targeted for completion in October
  - Asbestos, carbon tetrachloride and trichloroethylene targeted for completion by end of November